newandnoteworthy

Patent trends

In 2003, pharmaceutical and biotech patent owners were losers.

Of the 37 cases that went to appeal last year, lower-court juries favored defendants over patentees by a margin of 2 to 1, according to a biotechnology patent trends report by the intellectual property law firm Finnegan, Henderson, Farabow, Garrett & Dunner. Furthermore, the U.S. Court of Appeals for the Federal Circuit affirmed lower-court decisions in biotech patent cases 56% of the time and in generic versus branded drug cases 82% of the time.

Granted, the data has some flaws. In commentary within the report, Finnegan attorney Charles Lipsey notes a "statistical disadvantage" because "a relatively small fraction of issued patents ever get litigated, and among those that do, many settle before reaching final decision." Furthermore, the litigation survey, which queried the Westlaw ALLFEDS database, deals only with cases brought to appeal. Nonetheless, the findings are a source of concern.

"It seems potentially dangerous, if it is really the case, that patentees tend to lose as a matter of course, because it suggests a public bias against patents," says the report's editor, Arie Michelsohn, of the biotechnology/pharmaceutical practice group in Finnegan's Washington, DC, offices. "That is not good for a healthy, free, democratic American society."

The law firm also reported that there has been a leveling off of pharmaceutical and biotech patenting over the past few years, after explosive growth throughout the 1990s. This could be due to a number of factors, Michelsohn says, such as increasing challenges involved in getting patents through the Patent Office and more prudent decisions by companies about what patents they decide to pursue.

Overall, he hopes, the report will inform ongoing intellectual property policy debates. "Patents are at the forefront of the attention of the policymakers these days, and policymakers can generally benefit from empirical data."

—DAVID FILMORE

Stem cells: Screening for substrates

To probe for promising stem cell substrates, chemical and biomedical engineering professor Robert Langer and colleagues at the Massachusetts Institute of Technology (MIT) recently developed a miniaturized array for high-throughput cell–polymer interaction studies (*Nat. Biotechnol.* **2004,** *22,* 863–866).

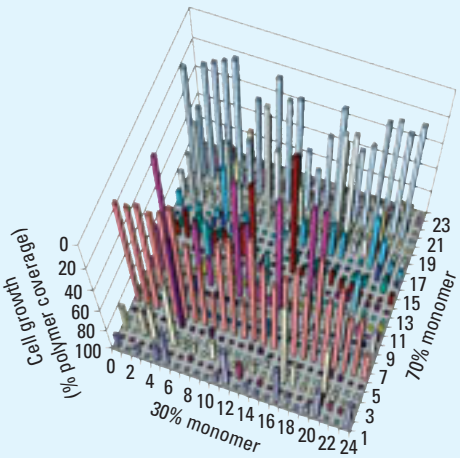
"Polymers can be used as surfaces for stem cell expansion and differentiation in vitro, as vehicles for encapsulation and delivery of therapeutic cells, and as scaffolds for tissue-engineered constructs," Langer says.

"Until now, there has been no quick, easy way to assess how a given material will affect cell behavior."

Since cells are highly sensitive to changes in their extracellular microenvironment, polymer surface properties can greatly affect cell growth and activity.

The MIT researchers modified a fluid-handling system to deposit in triplicate 576 combinations of 25 different acrylate, diacrylate, dimethacrylate, and triacrylate monomers onto a glass slide. Nanoliter-scale synthesis afforded a 1728-spot array of polymers that were screened against human embryonic stem cells stained for epithelial cytokeratin 7, mesenchymal vimentin, and DNA.

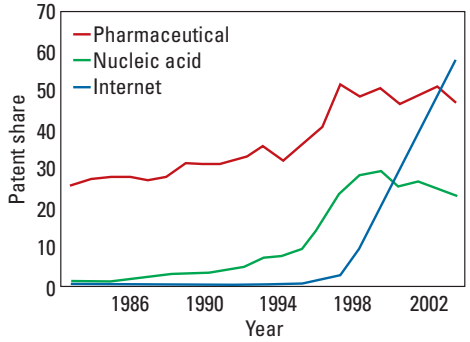
Most of the polymers allowed cell attachment and spreading, and a majority promoted cytokeratin-positive cells, suggesting, according to the researchers, that the materials might be good templates for producing epithelia. They believe this is the first method that allows the production of a "substantially pure" population of epithelia-like cells from human embryonic stem cells.



An array of possibilities. Researchers used cell-compatible arrays of acrylate polymers to identify biomaterials that support cell growth. (Adapted with permission from Anderson, D. G.; et al. *Nat. Biotechnol.* **2004,** *22,* 863–866.)

Embryonic muscle cells probed against a polymer array showed a different growth pattern, indicating, the team suggests, that scientists might be able to generate complex tissue-engineered products by adhering multiple cell types to a combination of polymers that promote differential growth and behavior characteristics.

—RANDALL C. WILLIS



Flattened patents. Pharmaceutical and biotech patenting has leveled off, according to a U.S. Patent and Trademark Office database. Patent share is the number of patents containing the search term per thousand total patents in a given year. (Source: *Biotechnology Innovation Report 2004: Benchmarks;* Finnegan, Henderson, Farabow, Garrett & Dunner: 2004.)

Chemical genomics initiative

To level the playing field between the pharmaceutical industry and academia, as well as fill niches not addressed by the corporate world, the NIH has established a Chemical Genomics Center. This facility is merely the first component of a nationwide network to develop "innovative chemical tools" for use in drug development and biological research.

Unlike their industry-based colleagues, academic and government researchers do not have ready access to vast libraries of small molecules that can be used to modulate gene function and improve basic understanding of molecular pathways involved in health and disease. Thus, to support the network, the NIH plans to create a repository to acquire, maintain, and distribute a collection of up to 1 million compounds.

"The NIH-supported chemical genomics network will have a transformative effect on medical research by expanding our understanding of how the human genome and proteome function," NIH director Elias Zerhouni explains. "This in turn will speed the development of new ways to fight disease and improve human health."

By the end of 2005, the network is expected to include up to 10 pilot centers at academic institutions and other locations across the country. According to National Institute of Mental Health director Thomas Insel, these centers will be coordinated across the academic community to identify a broad range of small molecules with "promising properties" for biological research.

Data generated by the project will be deposited in a central database called PubChem, which will be maintained by the National Center for Biotechnology Information and will be freely accessible to the entire scientific community. The inaugural center, which will be directed by National Human Genome Research Institute senior advisor for translational research Christopher Austin and staffed by about 50 scientists, plans to begin screening small molecules by the end of 2004.

Additionally, Jim Inglese, formerly a senior research fellow in automated biotechnology at Merck Research Laboratories, has been appointed head of biomolecular screening.

NATIONAL INSTITUTES OF HEALTH

I, Robot. Researchers at the new NIH Chemical Genomics Center will use robotic systems developed by Kalypsys to perform ultrahigh-throughput screening of small-molecule libraries.

The screening program will be facilitated by technologies developed by Kalypsys (*www.kalypsys.com*), a San Diego-based company specializing in ultrahigh-throughput and robotic instruments.

The agreement between the company and the NIH is valued at approximately $30 million and will extend over four years if all options are exercised.

—RANDALL C. WILLIS

Report to pharma: "Take the lead"

In a new study by Ernst & Young, its analysts challenge the pharmaceutical industry to take the lead when it comes to increasing its public credibility.

The report, entitled *Progressions: Global Pharmaceutical Report 2004*, details the complex challenges the industry is facing from a nervous Wall Street, consumer pressure on drug prices, and regulatory requirements. Despite improvements in early-stage pipelines on the horizon and progress in providing access to certain medicines in developing countries, the analysts say that "pharma is a convenient target for policymakers and the public in the U.S. and abroad." Therefore, the analysts say, better communication is a must.

"The industry needs to stand ready with something other than the standard response of, 'Our pharmaceutical products cost a lot, because it takes a lot to get them to market,'" Kathy Smith, Ernst & Young's Americas pharmaceutical sector leader, says.

Smith highlights the need for greater focus by companies on disease prevention as opposed to just disease management. "It's going to involve working with the providers, as well as a number of other constituents, to look for ways to detect disease early in its life cycle, and then use the knowledge that the pharmaceutical companies have for maintaining a patient on a given drug protocol," she explains

This will give a strong basis, she says, for the industry educating the public on the "cost-effectiveness" of its drugs.

Without such proactive measures, the report warns that political pressures might make government price controls and reimportation inevitable.

Another area where a proactive approach is essential, the report says, is keeping up with regulatory compliance. But on this front, Smith believes, good progress is beginning to be made. "The industry has taken great strides in managing [its] relationship with the FDA as well as other regulatory bodies outside the U.S."

"The spotlight here is more intense than ever before, and as a result, we're seeing a lot of activity," she notes. Executives and board members "recognize that severe or strict compliance with regulations is essential toward the trust with [the industry's] various stakeholders."

—DAVID FILMORE

Homing in on cancer

Research suggesting the lymphatic system may play a central role in cancer metastasis has led to a hunt for drugs that target tumor lymphatics for destruction. Researchers at the Burnham Institute, University of Helsinki, University of California at San Diego, and the biotechnology firm Anticancer have focused their efforts on the antitumor activity of the cyclic peptide LyP-1 (*Proc. Natl. Acad. Sci. U.S.A.* **2004,** *101,* 9381–9386).

The researchers intravenously injected fluorescently tagged LyP-1 into mice bearing human breast cancer xenografts and found a striking accumulation of the peptide in tumor-associated lymphatic vessels and tumor cells. Furthermore, they found that the targeting was specific to LyP-1—control peptides did not accumulate in the tumor-related tissues—and that LyP-1 targeting was specific to the tumor.

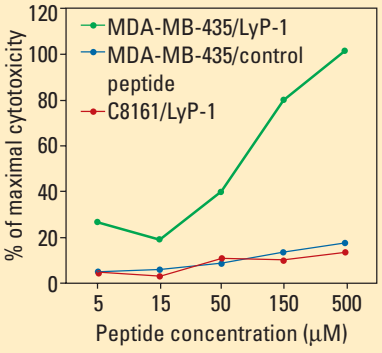
The researchers then tested the effect of LyP-1 on cancer metastasis by transfecting the tumor cells with a lymphangiogenic growth factor that promotes tumor growth. They found that LyP-1 accumulated in transfected cells at higher levels than in nontransfected cells, and they detected LyP-1 labeling in metastatic foci in lungs.

The researchers also noted that the LyP-1-positive cell clusters were similar to hypoxic cell clusters commonly found in tumors. They looked for a possible connection between LyP-1 binding and hypoxia, a promoter of metastasis, by co-injecting mice with a hypoxia-specific stain and LyP-1, and found that both labels occurred in the same tissues. Interestingly, at the level of individual cells, however, the staining was mutually exclusive, which indicates a possible common mechanism for uptake.

The researchers also noted that LyP-1-positive cells had the morphology of cells about to undergo apoptosis. When they incubated tumor cells in vitro with unlabeled LyP-1, they saw a concentration-dependent increase in cell lysis with an IC_{50} of ~66 µM.

They then tested the peptide's ability to inhibit tumor growth by injecting LyP-1 biweekly into xenograft mice with palpable tumors and found that within 4 to 5 weeks, the tumors in the treated mice had decreased by about 50% relative to the control mice. Likewise, they noted evidence of apoptosis and fewer lymphatic vessels in the treated sample.

Given these results, the researchers are confident that LyP-1-directed targeting of contrast agents can be useful in tumor detection and that the door is open for developing LyP-1-based treatments.



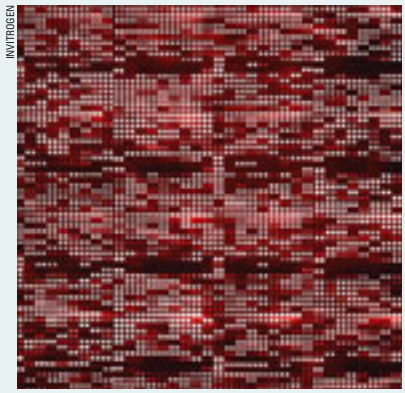
Targeted for termination. The nonapeptide LyP-1 triggers apoptosis in breast cancer cells (MDA-MB-435) but not melanoma cells (C8161). (Adapted with permission from Laakkonen, P.; et al. *Proc. Natl. Acad. Sci. U.S.A.* **2004,** *101,* 9381–9386. Copyright 2004 National Academy of Sciences, U.S.A.)

—RANDALL C. WILLIS

Protein array

Protein chips have hit the market. In June, Invitrogen announced the release of its Yeast ProtoArray, the first commercial comprehensive protein microarray for general research applications, according to the company.

Laboratory-produced chips have been put to limited use at least since 2000, when Harvard chemistry researchers Stuart Schreiber and Gavin MacBeath reported the development and testing of a protein microarray (*Science* **2000,** *289,* 1760–1763). But the Yeast ProtoArray offers the potential for broader accessibility and greater standardization.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Protein microarrays can be used for studies of high-throughput interactions with proteins, lipids, DNA, antibodies, and small molecules.

Each Yeast ProtoArray contains almost 5000 *Saccharomyces cerevisiae* proteins, double-spotted onto a surface-modified glass microscope slide, alongside several hundred internal and experimental controls.

Because 50% of yeast proteins have human counterparts, the organisms are commonly used to model basic human biology.

The chips are manufactured using proprietary techniques developed by Connecticut-based biotech firm Protometrix, which Invitrogen acquired in April. Bioinformatics programs are used to monitor and facilitate each step of the production process, and other tools, such as Western gel analysis, provide quality assurance measures for the chip's protein content.

"Protometrix has developed a unique technology that has the power to bring this next, and perhaps most productive, phase of the genomics and proteomics revolution into the mainstream of biomedical research and drug development," says Gregory Lucier, president and CEO of Invitrogen.

Using the same technology, Invitrogen plans to release a series of human protein microarrays later this year and, by 2006, a chip containing proteins representative of the majority of human genes.

"Invitrogen's comprehensive protein microarrays have the potential to answer questions that cannot be addressed by other technologies and to enable scientists to conduct research with novel proteins that have not been studied before," says Hollis Kleinert, president and CEO of Protometrix.

—DAVID FILMORE

U.S. FDA

CMS administrator McClellan

HHS teamwork

A recent agreement between the Centers for Medicare & Medicaid Services (CMS) and the National Cancer Institute (NCI) will make medical insurance reimbursement decisions more adaptive to progress in clinical cancer research, officials from the two Department of Health and Human Services agencies report.

A joint Memorandum of Understanding in development—focusing on specific areas of technology, science, and patient care where the agencies can work together—will also make CMS claims data more accessible for use as a tool in evaluating current technologies, the officials say.

"In taking these important concrete steps, we are moving the NCI–CMS partnership from an idea to a working reality that will make a difference for patients," says NCI director Andrew von Eschenback.

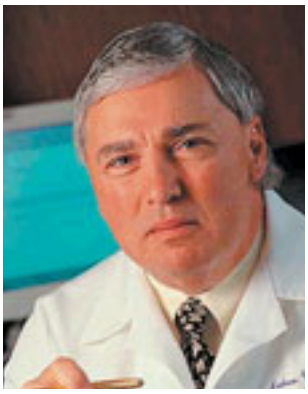
Developing a joint process for identifying high-priority clinical questions and addressing these questions in post-FDA approval clinical studies is one of the steps announced. In addition, the agencies will work to define a systematic process for cooperatively evaluating emerging diagnostic and therapeutic technologies to guide payment and coverage decisions.

CMS says it will engage NCI clinical experts "in all stages of national coverage determination development."

Sharing CMS data will also be an important part of the partnership. CMS has agreed to participate in NCI's cancer bioinformatics grid (caBIG), a diverse database of cancer research findings, and possibly include insurance claim data in the grid to make this information readily available for large-scale therapeutic outcome studies and comparisons.

"With so many new therapeutic options available to patients and doctors, and with patients becoming more active in their medical care, it's important that we make sure they have relevant and reliable information to support the choices they are making," says CMS administrator Mark McClellan.

NATIONAL CANCER INSTITUTE



NCI director von Eschenback

Besides the general aim of improving quality of care for cancer patients, CMS and NCI say their data- and resource-sharing efforts will address concerns such as decreasing disparities in cancer care across the population, and improving palliative and end-of-life care.

—DAVID FILMORE

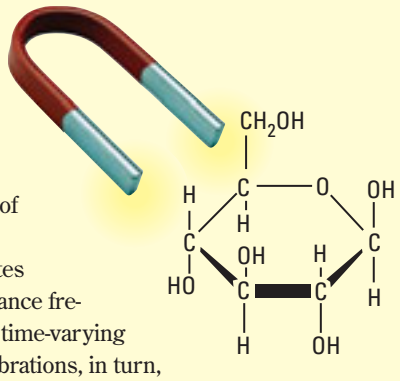
Diabetes: Magnetic monitor?

A new wireless magnetoelastic glucose sensor based on a pH-sensitive polymer offers the potential for in vivo and in situ diabetes monitoring, say its developers at Penn State and Boston University (*Anal. Chem.* **2004,** *76,* 4038–4043).

Diabetes mellitus is an increasingly prevalent burden on health care systems. Without careful monitoring of blood glucose levels to optimize insulin therapy and dietary control, chronic complications can occur.

Most electrochemical glucose sensors are based on the glucose oxidase-catalyzed conversion of the sugar to gluconic acid and hydrogen peroxide. To prevent glucose oxidase deactivation by hydrogen peroxide, catalase is often added.

Compounds such as uric acid and ascorbic acid, however, can interfere with sensor function because they can be oxidized or reduced at the working potential. Also, most sensors are placed in the skin, where the glucose that exchanges between blood and interstitial fluids is measured. However, there can be a lengthy delay between peak levels in blood and these fluids.



The wireless sensor developed by Penn State electrical engineering professor Craig Grimers, BU biomedical engineering professor Tejal Desai, and colleagues consists of a magnetoelastic ribbon that longitudinally vibrates at a characteristic resonance frequency in response to a time-varying magnetic field. These vibrations, in turn, generate a magnetic flux density that can be detected by a remote pickup coil. The researchers coated the ribbon with a pH-sensitive polymer and then immobilized glucose oxidase and catalase on the polymer layer through a bovine serum albumin intermediate. Thus, when glucose is oxidized at the ribbon's surface, it acidifies the surrounding environment.

The polymer responds to this drop in pH by shrinking, which reduces the magnetoelastic transducer's mass load and causes an increase in the resonance frequency. If the researchers desire, they can account for interfering analytes by cross-correlating the response to a reference sensor coated only with the pH-sensitive polymer.

In vitro, the researchers found that the sensor maintained its sensitivity and stability over several weeks and under a variety of electrolyte conditions. Likewise, they were able to calibrate the sensor to detect glucose over a range of 1–15 mmol/L, which encompasses the normal and diabetic ranges of 3.8–6.1 mmol/L and greater than 9 mmol/L, respectively.

There is potential for in vivo monitoring, the team suggests, because there is no need for a physical connection between sensor and monitor or an internal power source, but they have yet to test the sensor in humans.

—RANDALL C. WILLIS ■